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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/142,660	12/23/1998	RAINER HINTSCHE	60953/119	2492

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/142,660	HINTSCHE ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-25,27-34,37-40,42-46,50,53,54,59 and 62-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-25,27-34,37-40,42-46,50,53,54,59 and 62-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 23-25,27-34,37-40,42-46,50,53,54,59 and 62-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Attention is directed to the decision of *Vas-Cath Inc. v. Mahurkar* 19 USPQ2d 1111 (CAFC, 1991):

> This court in *Wilder* (and the CCPA before it) clearly recognized, and we hereby reaffirm, that 35 USC 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the "applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

3. For convenience, claims 44 and 66, the only independent claims, are reproduced below.

44. (Amended) A method of detecting a molecule or molecular complex in a sample, comprising:

(a) contacting the sample comprising a first molecule or a first molecular complex with a single ultra-microelectrode array, said ultra-microelectrode array comprising at least two electrode structures,

(b) producing an electric field between the electrode structures; and

(c) measuring changes in current or potential between the electrode structures, whereby the changes in current or potential are caused by the first molecule or the first molecular complex,

wherein said first molecule or molecular complex is a third polynucleotide that hybridizes to a second polynucleotide that is hybridized to a first polynucleotide, wherein said first polynucleotide is bound to a binding compound on said ultra-microelectrode array; and

wherein each of said electrode structures is insulated from each other and is either a layer on a planar insulating support material or is incorporated in said planar insulating support material; and

wherein the spacing between the electrode structures is about 1 μm or less; and wherein the electrode structures are arranged so closely next to one another that they approach the size of large molecule complexes.

–63. (New) A method of detecting a first molecule or a first molecular complex in a sample, comprising:

(a) contacting the sample comprising a first molecule or a first molecular complex with a single ultra-microelectrode array, said ultra-microelectrode array comprising at least two electrode structures;

(b) producing an alternating electric field between the electrode structures;

(c) measuring changes in current or potential between the electrode structures, whereby the changes in current or potential are caused by the first molecule or the first molecular complex; and

(d) detecting the presence of said first molecule or first molecular complex by observing said change in current or potential;

wherein said first molecule or first molecular complex is selected from the group consisting of nucleic acids, peptides and proteins; and

wherein each of said electrode structures is insulated from each other and is either a layer on a planar insulating support material, or is incorporated in said planar insulating support material and wherein the spacing between the electrode structures is about 1 μm or less; and

wherein the electrode structures are arranged so closely next to one another that they approach the size of large molecule complexes.

4. For purposes of examination, claims 44 and 66 have been interpreted as encompassing the embodiment where "the electrodes structures are arranged so closely next to one another that they approach the size of large molecules." Page 8 of the response of 17 April 2003 directs attention to where support for the claim language can be found. While agreement is reached in that the specification does provide support for the claim language, said newly added claim language fairly reads on an embodiment where two or more electrodes are in effect brought so closely together that the actual electrodes undergoes molecular collapse akin to that of a black hole such that together "they approach the size of large molecules." A review of the specification fails to find an adequate written description of where such an effect has been

achieved. Indeed, the examiner is unaware of where any molecule, be it an electrode of not has been so reduced in size through the hand of man.

5. Accordingly, and in the absence of convincing evidence to the contrary, the specification does not provide an adequate written description of the claimed invention such that it reasonably suggests that applicant possessed the invention at the time of filing.

6. Claims 23-25, 27-34, 37-40, 42-46, 50, 53-54, 59, and 62-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737,

> 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

7. For purposes of examination, the claimed method has been interpreted as encompassing the detection of any nucleic acid, protein, and peptide molecule or molecular complex, even when such is present in a highly heterogeneous mixture, be it desiccated or liquid, and where the solvent, if any, can have any potential and be of any viscosity.

8. Claims 66-69 require the electrode to be manufactured of specific substances. Claims 64 and 73 further require that the "first molecule or first molecular complex" (any nucleic acid, protein or peptide or mixture that comprises same) be "positioned in the gap by chemical binding, adhesion, or condensation reactions." For convenience, said claims are reproduced below.

> 64. A method according to claim 35, wherein the first molecule or first molecular complex is positioned in the gap by chemical binding, adhesion, or condensation reactions.

66. The method of either claim 63, wherein a surface of the electrode structures comprises a layer of conductive material, said material being selected from the group consisting of a noble metal, a carbon material and both a noble metal and carbon material.

67. The method of 63, wherein said ultra-microelectrode array is a noble metal or a carbon material or comprises said noble metal or carbon material.

68. The method of claim 66, wherein said noble metal is selected from the group consisting of gold, platinum and iridium.

69. The method of claim 67, wherein said noble metal is selected from the group consisting of gold, platinum and iridium.

73. (New) A method according to claim 72, wherein the first molecule or first molecular complex is positioned by chemical binding, adhesion, or condensation reactions.--

9. A review of the specification fails to find any example, including prophetic, where reaction conditions and starting materials are disclosed whereby any nucleic acid has been detected. Additionally, the specification is essentially silent as to how any nucleic acid, protein or peptide is to be detected when it is part of a heterogeneous mixture. The presence of other materials, especially of like or smaller size could also be placed within the gap between the electrodes and alter the perceived change in current or potential. The specification is also silent as to how one is to position the nucleic acid, protein or peptide by "chemical binding, adhesion, or condensation reactions" when the electrode is manufactured of any material, and not just the materials recited in claims 66-69.

10. In addition to teaching how to use or practice a given method, the specification must also enable one of skill in the art to make the invention, which in the resent case are the electrode arrays. As shown above, the electrode arrays are to be comprised of any of a variety of substances. The specification is essentially silent as to how the electrode structure is to be manufactured such that it is readily used in the claimed method. Accordingly, the burden of enablement is unfairly shifted from applicant to the public.

11. Claims 24 and 27 place restrictions on the measurement of changes in current (claim 24) and what the electric field is comprised of (claim 27).

24. (Amended) A method according to claim 63, wherein the changes in current or potential are measured independently of time, as a function of time or as a function of the phase angle of the current.

27. (Amended) A method according to claim 63, wherein the alternating electric field comprises, is superimposed, or excited with a direct-current component.

12. A review of the specification fails to find any teaching whereby one of skill in the art at the time the invention was made would be able to determine just when and how the current or potential is "measured independently of time, as a function of time or as a function of the phase angle of the current" and to then extrapolate such measurements into a meaningful result which indicates the presence or absence of any nucleic acid, protein, or peptide.

13. The specification does state at page 14 that in a prophetic example, detection of the complex was "carried out with the function of the β-galactosidase." Such detection is completely different from what is being claimed.

14. Acknowledgement is made of applicant's argument of 09 January 2003 where attention is directed to various prior art articles and a website (see pages 8-9 of the response of 09 January

2003) as showing that impedance spectroscopy is old in the art. Such showings, however, do not fill the void of instructing the public as to how such technology is to be modified or adapted such that it could be applied in the instant method which applicant asserts to be both novel and non-obvious.

15. Acknowledgement is made of where at page 8 of the response of 09 January 2003 attention is directed to the Rule 1.132 declarations filed with the response of 27 August 2001. Said declarations were considered on the record in the Office action of 18 September 2001. For convenience, that portion of the 2001 Office action is reproduced below.

16. Upon review of the declaration of Dr. Rainer Hintsche and Dr. Manfred Paeschke it is noted that the declarants are also the inventors and as such have a vested interested in the outcome of the examination of the subject application. The declaration is found to contain the opinion of both with assertions that one of ordinary skill in the art could readily adapt prior art methods so to enable the claimed invention. Attention is directed to non-patent literature as well as to foreign patents and to two US patents.

17. The above arguments have not been found persuasive towards the withdrawal of the rejection for as stated in the decision of Genentech:

> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. <u>However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art.</u> It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This

> specification provides only a starting point, a direction for further research. (Emphasis added)

18. Declarants have not shown how the specification fully enables the full scope of the claims without forcing the public to resort to undue experimentation. The aspect of world patent documents or PCT applications being published is immaterial to the present issue of enablement as they are not US patents. Even in the case of US Patents 5.572,256 and 5,653,939, such publications do not have any bearing on the present application as each application is considered on its own merits. Accordingly, the opinion declaration of Dr. Rainer Hintsche and Dr. Manfred Paeschke has not been found persuasive towards the withdrawal of the rejection.

19. The second declaration presented is also that of co-inventor Dr. Rainer Hintsche and as such declarant is recognized as having a vested interest in the prosecution of the subject application. The Declaration presents experimental examples with detailed explanation as to how the four examples were conducted. Said examples are found to contain bibliographical reference to numerous non-patent publications were relied upon in practicing the examples, a review of the disclosure of the subject application does not find that these prior art publications were relied upon for enablement. The examples presented in the declaration so to demonstrate enablement are not commensurate in scope with the disclosure of the subject application. Accordingly, and in the absence of convincing evidence to the contrary, the declaration has not been found to be persuasive towards the withdrawal of the rejection.

20. The specification fails to overcome art-recognized difficulties. US Patent 6,391,624 B1 (Megerle) teach:

> Although this technique is both highly accurate and rapid, it nevertheless requires a sufficient sample available in the hybridization mixture to make detection measurements

> and, when the number of hybridized pairs of the modified molecules is very low, the presence of the target DNA is difficult to detect. When the number of hybridized pairs is very low, electrical current flowing between the electrode and through the electron donor or acceptor group may be to low for the electrical circuitry of the detection device to detect. In addition to the sensitivity problems which are inherent when only small samples are available to test, the sensitivity of probes using hybridization techniques are further adversely affected by steric hindrance of the target nucleotide molecules. In this regard, when the relatively long molecules of denatured single stranded DNA bind with the oligonucleotides attached to the electrode, segments of the molecule on the free ends which did not bind may physically interfere with the ability of additional molecules to hybridize with neighboring oligonucleotides. (Emphasis added)

It is noted with particularity that the specification is effectively silent as to how low concentrations of nucleic acid, polypeptides, or peptides are to be detected. Indeed, the claimed method fairly encompasses detecting but a single molecule that is present in a sample.

In view of the breadth of the claims, the limited disclosure provided, and the unpredictability of the art, the specification is deemed not to enable the claimed invention. Accordingly, claims 23-25, 27-34, 37-40, 42-46, 50, 53-54, 59, and 62-70 are rejected under 35 U.S.C. 112, first paragraph, as not being enabled by the disclosure.

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 23-25, 27-34, 37-40, 42-46, 50, 53-54, 59, and 62-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. Said claims are indefinite with respect to just what constitutes the metes and bounds of "large molecular complexes."

24. Claim 23 provides for the use of impedance spectroscopy, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

25. Claim 23 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd. App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

26. Acknowledgement is made of applicant's traversal of the instant rejection; see page 11 of the response of 09 January 2003. While agreement is reached in that the step does comprise a method step for another method, the step so provided is the "use" f a product. The claim does not recite just how this "use" is to be affected. Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 101

27. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

28. Claims 23-25, 27-34, 37-40, 42-46, 50, 53-54, 59, and 62-70 are rejected under 35 U.S.C. 101 because the disclosed invention is inoperative and therefore lacks utility. As presently worded the claimed methods require the "electrode structures" to be reduced in size to where the overall structure "approach[es] the size of large molecule complexes" and that one is

to subsequently be able to detect the presence of first molecule or first molecular complex through changes in current or potential between the electrodes. It is not possible, except in a black hole, for matter to be compressed. The office is unaware of such forces being effectively reproduced by the hand of man, and even if they could be, the "first molecule or first molecular complex" would not be able to fit within the space between the electrodes such that there would be any change in current or potential to measure.

Claim Rejections - 35 USC § 103

29. In view of the amendments to the claims, the rejection of claims under 35 USC 103(a) is herby withdrawn.

Conclusion

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

31. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (703) 308-3978. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (703) 308-1119. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

34. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS